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Pathophysiology, Diagnosis and Clinical Management of Hepatorenal Syndrome: From Classic to New Drugs

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Abstract: Advanced cirrhosis is frequently associated with renal dysfunction. Hepatorenal syndrome (HRS) is characterized by the occurrence of kidney injury in cirrhotic patients in the absence of other identifiable causes. HRS is classified in 2 different types. Type 1 is characterized by acute renal failure and rapid functional deterioration of other organs, usually related to a precipitating event. Type 2 is characterized by slowly progressive renal failure and refractory ascites. Advanced liver disease induces the progression of hemodynamic alterations such as arterial vasodilation of splanchnic circulation and impairment of cardiac function. The resulting ineffective circulating blood volume promotes the activation of both the renin-angiotensin-aldosterone and sympathetic nervous system, by an increase of antidiuretic hormone activity, in an attempt to restore volemia. Despite fluid retention, ascites and dilutional hyponatremia, renal function is often initially preserved by renal production of vasodilators. However, further insults can lead to an imbalance between systemic vasoconstriction and local renal vasodilation, resulting in progressive renal failure. Over the last decade, clinical strategies to prevent HRS have been improved by a better understanding of the natural history of renal failure in cirrhosis, resulting in a reduction of HRS prevalence in cirrhotic patients. Vasoconstrictor drugs may improve renal function, but the effect on mortality has not yet been established. Vaptans, nonpeptide vasopressin receptor antagonists, may also reduce hyponatraemia and ascites, even if the clinical effects in HRS remain unknown. This review updates the pathophysiology, diagnosis and management of HRS.

Keywords: Acute kidney injury, hepatorenal syndrome, refractory ascites, terlipressin, vaptans, vasoconstrictors.

INTRODUCTION

Hepatorenal syndrome (HRS) represents a life threatening complication of advanced liver failure. The hemodynamic dysfunction may progress to HRS through several stages in accord with the evolution of liver disease [1, 2]. Diagnosis of HRS is based on criteria established in 2007 by International Ascites Club (IAC) [3] (Table **1**).

HRS: CLINICAL PRESENTATION

Type 1 HRS is characterized by an acute kidney failure and a rapid increase in plasma creatinine levels to more than 2.5 mg/dL and doubled in less than 14 days [2-4], though urine volume may be not reduced or may even be normal. The majority of patients have features of advanced liver disease, such as edema, ascites, coagulopathy, low albumin levels, hepatic encephalopathy, jaundice, poor nutritional status or signs of acute-on-chronic liver failure [4]. Type 1 HRS may be an expression of multiorgan failure, overlapping with other causes of acute kidney injury [5]. Arterial hypotension and low systemic vascular resistance are typical features of circulatory dysfunction [6]. A challenge for physicians is the differential diagnosis in cirrhotic patients between sepsis and type 1 HRS, to the point that in suspected HRS patients need to be checked for signs of infection [7]. Moreover, type 1 HRS usually occurs in relation to a triggering event, mainly represented by an infective episode such as ***spontaneous bacterial peritonitis*** (SBP) [8, 9].

The main difference between type 1 and ***type 2 HRS*** is the different progression of renal damage. Kidney disease of type 2 HRS patients may remain stable for long periods or have a typical slow progression with moderate-severe renal impairment. Clinically, it is important to stress that the *kidney problem* is usually less significant than the *ascites problem* in type 2 HRS patients, because the reduced glomerular filtration rate (GFR) associated with sodium retention, hyperaldosteronism and activation of sympathetic system promote a multifactorial resistance to diuretics (Table **2**).

Furthermore, a type 2 HRS may overlap and turn in type 1, usually because of a triggering complication such as an infection. Type 2 HRS has a better prognosis than type 1, with 3-month survival of 40% and 20%, respectively [10] and longer survival expectancy [11].

PATHOPHYSIOLOGY OF RENAL FAILURE

HRS represents a functional syndrome, as suggested by the absence of morphologic abnormalities in renal histology [12], the normalization or improvement of kidney function after liver transplant [13] and the syndrome reversibility by

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Table 1. Hepatorenal Syndrome (HRS) International Ascites Club (IAC) criteria (2007)[3].

HRS IAC criteria	
Cirrhosis in absence of ascites	Absence of shock
Serum creatinine > 1.5 mg/dL	Absence of nephrotoxic drugs administration
No improvement of serum creatinine (decreased < 1.5 mg/dL after 2 days off diuretics and volume expansion with albumin)	No signs of parenchymal renal disease (*e.g.* proteinuria > 500 mg/24h, hematuria or abnormal renal ultrasound)

Table 2. Type 1 and type 2 Hepatorenal Syndrome (HRS) features.

	Type 1 HRS	Type 2 HRS
Course	Acute (Doubled serum creatinine in <14 days)	Progressive
Triggering event	Present in >50% of patients	Usually absent
Diuretic resistant ascites	Present in <50% of patients	Always present
Prognosis (3-month survival)	20%	40%

pharmacologic treatment [14]. The following is a summary of the current understanding of the pathophysiology of HRS.

Portal Hypertension and Hemodynamic Changes

Systemic vasodilation is the predominant haemodynamic alteration in portal hypertension. In the early stages of liver disease, both the intrahepatic vascular resistance and portal hypertension are moderate, because of fibrosis and dysfunction of liver endothelial cells associated with vasodilation of splanchnic arteries. Moreover, in presence of moderate portal hypertension, the arterial pressure and the effective arterial blood volume remain within normal limits because increased cardiac output compensates for a modest reduction in systemic vascular resistance [15]. Conversely, in advanced stages of cirrhosis, systemic vascular resistance is markedly reduced, and the additional increase in cardiac output cannot compensate, leading to underfilling of the arterial circulation [15]. Contributory factors in the reduction of splanchnic vascular resistances are the neoangiogenesis of mesenteric arteries and an impaired response to vasoconstrictors [2].

Either singly or in concert, several mediators may be responsible for splanchnic and systemic vasodilation.

Nitric oxide (NO) is synthesized by several cell types, including endothelial and vascular smooth muscle cells, causing vasodilation [16]. In patients with decompensated cirrhosis, the increased levels of plasma nitrite/nitrate are the result of a corresponding increase of NO production [17].

Prostacyclin is a systemic vasodilator and its secretion is stimulated by shear stress in the arterial system [18, 19]. Urinary excretion of both systemic and renal metabolites of prostacyclin is high in decompensated cirrhosis, and plasma levels (undetectable by available analytical methods) are presumably elevated [20, 21]. However, in severe hepatic decompensation and in HRS, the excretion of renal and systemic prostanoids is not different and, therefore, it is unlikely that prostacyclin plays a key-role in the development of HRS.

Activation of potassium channels can cause vasodilation due to hyperpolarisation of vascular smooth muscle cells, promoted by potential activators such as tissue hypoxia, prostacyclin, neuropeptides and NO. In fact, because the baseline vasodilatative tone depends on potassium channels, the administration of potassium channel blockers significantly increases vascular portal and systemic resistance, showing a possible contributing role of these channels in cirrhosis [22, 23].

The progressive decrease in arterial resistance in the splanchnic circulation is associated with an unrelenting reduction in total systemic vascular resistance. In the scenario of extreme underfilling of arterial circulation, the body maintain arterial pressure by activating vasoconstrictor systems, including the sympathetic nervous system, renin-angiotensin system and, in late stages, non-osmotic hypersecretion of arginine vasopressin [15]. On the one hand, these mechanisms preserve the effective blood volume and arterial pressure; on the other they strongly influence kidney function, particularly retention of sodium and solute-free water. As consequence, ascites and edema develop, as well as hypervolemic hyponatremia. If the vasoconstriction systems are activated to a high degree, renal vasoconstriction occurs, leading to decreased GFR and the development of HRS [14, 15, 24].

Spontaneous Bacterial Peritonitis (SBP)

SBP represents a dangerous manifestation because of high mortality rate especially when undiagnosed. About half of SBP are present at the time of admission to the hospital, while the others are acquired during hospitalization. Clinically SBP is characterized by signs of peritonitis, systemic

inflammation, worsened liver function, hepatic encephalopathy or shock.

In patients with SBP, renal failure is a common and particularly severe feature and in these cases, the main mechanism promoting peritonitis is represented by ***bacterial translocation*** from the intestinal lumen to mesenteric lymphnodes and internal organs [25, 26]. The bacterial infection causes a severe inflammatory response in the peritoneal cavity, promoting an increase of proinflammatory cytokines and lasting production of vasoactive mediators (such as NO) [27, 28].

Thus, ***inflammation*** had a primary role in course of SBP. In fact, in ascitic fluid of SBP patients, the levels of proinflammatory cytokines, such as interleukin 1-β (IL-1 β), tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) are higher than in cirrhotic controls. Moreover, the ascitic fluid levels of cytokines decreased rapidly after infection resolution [29].

Bacterial translocation promotes circulatory dysfunction. In fact, the administration of an antibiotic, such as norfloxacin, which selectively decontaminate the intestinal tract, leads to an improvement of circulatory function and reduces the risk of developing HRS [30, 31].

Experimentally, systemic hemodynamics are not influenced by bacterial endotoxins in healthy controls, whereas it induces arterial hypotension and increases plasma levels of cytokines (TNF-α and IL-6) in patients with cirrhosis and ascites [32]. Any type of bacterial infection may cause kidney dysfunction in patients with cirrhosis, but the severity of inflammatory response and renal impairment are lower than in SBP [33].

Renal Vasoconstriction

Renal hemodynamics are based on a delicate balance between intrarenal vasoconstrictors and vasodilatative agents.

The early stages of liver disease are associated with renal and systemic hemodynamic changes, even in absence of laboratory alterations of renal function, such as creatinine. Furthermore, in cirrhotic patients the intrinsic renal function remains stable, even in presence of marked renal vasoconstriction [9, 10] and decreased GFR [11]. In fact, explanted kidneys from patients who expired because of HRS have been successfully transplanted in patients with renal failure [11, 12]. In addition, both optimal medical therapy and liver transplantation are able to reduce renal sodium retention and kidney impairment in HRS, as additional evidence of normal intrinsic renal function.

Patients with advanced liver disease have circulatory dysfunction and arterial underfilling associated with increased intrarenal endogenous vasoconstrictor activity.

Renal autoregulation prevents fluctuations in renal blood flow (RBF), ensuring a stable RBF during changes in renal perfusion pressure above 70-75 mmHg. Below these values, RBF is directly proportional to perfusion pressure [34]. The synthesis of several renal vasoconstrictors is increased in patients developing HRS, making RBF much more pressure dependent. Thus, modest decreases of blood pressure may result in marked reduction of RBF [35].

The pathogenesis of HRS is influenced by the increased synthesis of several vasoactive factors acting on the intrarenal circulation, such as thromboxane A2, cysteinyl leukotrienes, F2-isoprostanes and endothelin [36].

In patients with cirrhosis the overall reduction in renal vasodilator production, promotes renal vasoconstriction and stimulate the production of various intrarenal agents including angiotensin II and endothelin [7, 37, 38].

The possible role of ***renin-angiotensin system*** is suggested by the decrease in portal pressure in patients with cirrhosis and portal hypertension [39, 40] when administered with an angiotensin II receptor antagonist, such as losartan. Moreover, the vascular dependence on angiotensin II in severe cirrhosis indicates that this mechanism contributes to vascular dysfunction.

The production of ***vasopressin*** is promoted by non-osmolar stimulation, despite the frequent presence of hyponatraemia in the course of HRS [41, 42]. Vasopressin acts through V1 and V2 receptors, causing respectively vasoconstriction (preferentially in splanchnic rather than renal vascularization) and renal tubular water retention in the medullary collecting ducts.

A major role in the preservation of kidney function is ensured by ***renal prostaglandins***, especially in clinical situations such as dehydration, congestive cardiac failure, shock and decompensated liver disease. In fact, in HRS the renal prostaglandin E2 and prostacyclin levels as well as their urinary metabolite excretion are decreased compared with patients with ascites alone [43].

In conclusion, the alteration of balance of intrarenal vasoactive agents may promote further impairment of renal hemodynamic and kidney function, occasionally with glomerular ischaemia and mesangial constriction [44].

Sympathetic Nervous System

The activation of sympathetic nervous system in patients with HRS promotes the secretion of catecholamines, renal vasoconstriction and sodium retention [45, 46]. In fact, transjugular intrahepatic portosystemic shunt (TIPS) allows controlling portal hypertension by reducing sympathetic nervous activity and improving RBF [47, 48]. In contrast, the infusion of glutamine is able to increase hepatic sinusoidal pressure, mimicking portal hypertension, and to reduce the GFR [49]. Finally, the renal sympathetic activity increases RBF when lumbar sympathetic blockade is performed in patients with HRS [50].

Cirrhotic Cardiomyopathy

Cirrhotic cardiomyopathy is a condition associated to a relative inability to increase cardiac output during stress [51] and represents a risk factor for HRS development [52]. The diagnosis of cirrhotic cardiomyopathy results from a combination of electrocardiography, echocardiography and different serum markers in absence of cardiac disease.

In cirrhotic patients several ***electrophysiological abnormalities*** have been observed, such as chronotropic incompetence, electromechanical uncoupling and prolonged QT in-

terval. On ***echocardiography***, cirrhotic cardiomyopathy is characterized by signs of both systolic and diastolic dysfunction [53]. Among ***serum markers***, Brain Natriuretic Peptide (BNP) and pro-BNP are well-known markers of early stage heart disease, associated with both the severity of cirrhosis and the degree of cardiac dysfunction in course of liver disease [54]. Levels of cardiac troponin I are typically slightly increased in cirrhosis in absence of other known heart disease, as expression of underlying cardiac injury [55].

Management of cirrhotic cardiomyopathy is generally similar as in non-cirrhotic patients. ***Beta-adrenergic blockade*** may improve QT interval, by reducing the portal pressure and the shunt of cardiotoxins from splanchnic circulation [56].

In preascitic cirrhosis, the anti-fibrotic action of ***aldosterone antagonists*** may be helpful to reduce the parietal wall thickness of the left ventricle and the circulatory volume load, with potentially favorable effects on myocardial hypertrophy and diastolic dysfunction [57].

All the above factors contribute to the gradual deterioration in renal function as cirrhosis advances. The events causing an abrupt deterioration in hemodynamics may lead to a rapid decline in renal function, precipitating type 1 HRS.

Finally, in some cirrhotic patients with cirrhosis, intrinsic renal nephropathies may be related not to alterations in systemic hemodynamic but rather to the etiologic factors underlying the liver disease, such as glomerulonephritis associated with hepatitis B or C and alcoholic cirrhosis [58, 59].

MANAGEMENT OF HRS

Prevention of HRS

Cirrhotic patients with ascites at risk for HRS should be carefully monitored and treated [60].

Type 1 HRS usually occurs in relation to a precipitating events such as SBP, viral infections and non-infectious events (alcoholic, toxic or ischemic hepatitis, gastrointestinal bleeding and major surgical procedures). However, in some cases, a precipitating event cannot be identified [13, 36].

HRS develops in approximately 30% of patients with SBP. Three different patient populations have been identified for the onset of SBP: (1) patients with acute gastrointestinal bleeding, (2) patients with low total proteins in ascitic fluid and no prior history of SBP (primary prophylaxis), and, (3) patients with a previous history of SBP (secondary prophylaxis) [1].

Bacterial infection should be identified early by blood, urine or ascitic fluid cultures and treated with antibiotics. Patients who do not have signs of infection should continue taking prophylactic antibiotics, if previously prescribed [1].

Prophylactic antibiotics prevent bacterial translocation and suppress pro-inflammatory cytokine production implicated in the pathogenesis of HRS [5, 61, 62]. Antibiotic therapy suggested as primary prophylaxis of SBP in patients with ascites and severe liver failure (Child-Turcotte-Pugh score ≥9 and serum bilirubin >51 μmol/L) or renal failure (serum creatinine ≥106 μmol/L or serum sodium ≤130 mmol/L) are norfloxacin or ciprofloxacin eventually in association with trimethoprim-sulfamethoxazole [34, 63].

Nosocomial mortality and the risk of developing HRS were lower in patients receiving albumin in association with antibiotic compared with those who received an antibiotic alone (10 *vs* 29%). An initial dose of albumin of 1.5 g/kg is administered at diagnosis of infection, followed after 48 h by a further infusion of 1 g/kg [64].

The mechanisms by which albumin prevents HRS are incompletely understood but may be related to positive effect of albumin on circulatory function and its antioxidant properties [65, 66].

Gastrointestinal bleeding should be another precipitating event which can cause renal failure in 11% cirrhotic patients [67]. Risk factors for renal failure in these patients include the severity of blood loss and the degree of liver failure. In patients with alcoholic hepatitis, the administration of prophylactic pentoxifylline (a TNF-α antagonist, 400 mg 3 times daily for 28 days) was associated with lower risk of HRS and lower mortality [68, 69].

Some nephrotoxic drugs have been reported to precipitate HRS and should be avoided (Table **3**) [25].

Non-steroidal anti-inflammatory drugs (NSAIDs), reducing renal perfusion secondary to inhibition of renal prostaglandin synthesis, are contraindicated in patients with ascites because of the high risk of developing sodium retention, hyponatremia and renal failure [70].

Angiotensin-converting enzyme inhibitors (ACEi), even in low doses, should be avoided in patients with cirrhosis and ascites because can induce arterial hypotension and renal failure [1].

Alpha blockers, such as prazosin, are responsible of a reduction in portal pressure and should be used with caution. These drugs can further impair renal sodium and water retention and cause an increase in ascites and/or edema [1].

Aminoglycosides alone or in combination with ampicillin, cephalothin, or mezlocillin should be avoided in the treatment of bacterial infections because they are associated with nephrotoxicity [1, 15].

In cirrhotic patients ***contrast media*** are frequently administered in radiological procedures. Contrast media may induce acute renal failure in general population as well as in cirrhotic patients, especially in presence of kidney disease [71].

General Management Strategies

When renal failure occurs, assessment for liver transplantation should start as soon as possible.

The ideal goals of treatment for HRS are prolonged survival and to achieve optimized clinical conditions for successful liver transplantation [5].

Type 1 HRS patients waiting for liver transplant are generally better managed in an intensive or semi-intensive care unit, because multi-organ failure may rapidly and abruptly complicate the clinical course [1, 72]. Patients with type 2

Table 3. Drugs contraindicated in patients with ascites.

Renal insult	Mechanism	Drug
Reduced systemic Blood pressure	Reduced intra-renal Perfusion pressure	Alpha-blockers Angiotensin-converting enzyme inhibitors
Reduced glomerular Perfusion	Inhibition vasodilatory renal prostanoids Glomerular vasoconstriction	Non-steroidal anti-inflammatory cyclooxygenase-2 inhibitors Dipyridamole
Nephrotoxicity	Renal tubular toxicity	Aminoglycosides Amphotericin Radiocontrast media

HRS without associated complications are managed as out-patients [2].

In addition to standard vital signs, general parameters to be assessed include urine output, fluid balance and arterial pressure. Moreover, a central venous catheter is important to evaluate central venous pressure, helping in the management of fluid balance and in prevention of volume overload. Because bladder catheterization is associated with urinary tract infections, this procedure should be limited to cases of marked oliguria [72].

Use of Diuretics

Renal failure occurs in 30% of cirrhotic patients treated with diuretics [73] and 2 different types are described. The first occurs in patients in diuretic treatment after complete resolution of ascites and renal failure is determined by dehydration and hypovolemia. The second type is observed in patients with ascites related to compartmentalization of edema and maximum reabsorption capacity of lymphatic vessels with consequent hypovolemia and renal failure [66]. In patients with recurrent ascites a combination of an aldosterone antagonist and furosemide, eventually with increasing dose in according to response is indicated [1]. The maximum recommended weight loss during diuretic therapy should be 0.5 kg/day in patients without edema and 1 kg/day in patients with edema [1]. The goal of long-term treatment is to maintain patients free of ascites with the minimum dose of diuretics. Thus, once the ascites has largely resolved, the dose of diuretics should be reduced and discontinued later, whenever possible.

Diuretics in patients with renal impairment, hyponatremia, or alterations in serum potassium concentration should be administrated with caution, because hypovolemia and renal failure may develop if urine volume is more than the body maximum capacity of ascites reabsorption.

All diuretics should be discontinued in presence of severe hyponatremia (serum sodium concentration <120 mmol/L) and progressive renal failure.

Serum potassium levels should be corrected before the administration of diuretic therapy [1, 3]. Contraindication to furosemide administration is severe hypokalemia (<3 mmol/L), whereas aldosterone antagonists should be stopped in presence of severe hyperkalemia (serum potassium >6 mmol/L).

Paracenteses

Large ascites should be treated with repeated paracenteses associated with intravenous administration of albumin (8 g/l of ascites removed) [73]. Large-volume paracentesis (LVP) >5 L of ascites is associated to a high risk of developing post-paracentesis circulatory dysfunction. After LVP, patients should still receive albumin and the minimum dose of diuretics, as prevention of recurrent ascites [1].

The use of colour-Doppler ultrasound has shown that paracentesis reduced intra-renal pressure with improved diastolic perfusion [74]. The majority of patients (60-70%) treated by paracentesis alone, without volume expansion with albumin, develop an impairment in circulatory function, related to increased splanchnic arterial vasodilation. The administration of albumin is very effective as prevention of this complication [75].

In a randomized controlled clinical trial, albumin infusion reduced both HRS incidence and mortality, when started at initial dose of 1 g/kg of body weight and up to a maximum of 100 g, followed by 20-40 g/day. In contrast, synthetic plasma expanders are not recommended after high volume paracentesis (>5 L) because they are less effective in HRS prevention [76].

Administration of Fluids

Cirrhotic patients often have a hyperdynamic circulation characterized by increased cardiac output, systemic hypotension and reduced peripheral vascular resistance [1]. Optimizing intravascular volume is essential in patients affected or at risk of developing HRS [77].

An excessive administration of fluids may promote an increase in ascites, in central venous pressure and risk of pulmonary edema [2].

Assessment of intravascular volume in HRS is complicated and standard measurements such as central venous pressure (CVP) and pulmonary capillary wedge pressure show a poor relationship with blood volume; also, these measurements may be difficult because of the bleeding risk [78, 79]. In HRS patients treated with an infusion of 20% albumin, a significant increase in central blood volume and cardiac index was observed without changes in CVP [72]. In patients with cirrhosis, volume expansion with albumin administration has been shown to reduce plasma renin levels, suggesting an improvement in the effective circulating volume [80].

SPECIFIC MANAGEMENT OF TYPE 1 HRS

Treatment of type 1 HRS should be started quickly to prevent the progression of renal failure. Splanchnic arterial vasodilation is the main mechanism in the pathogenesis of HRS and thus the administration of vasoconstrictors drugs is considered the best therapy to improve circulatory function.

Moreover, vasoconstrictors (octreotide with midodrine, norepinephrine and terlipressin) in association with albumin improve renal function in 40-60% of type 1 HRS patients, compared with vasopressors alone [1, 81], because of an increase in mean arterial pressure and vasoconstrictor activity suppression [82].

Serum bilirubin concentration <171 μmol/L and an increase in mean arterial pressure of >5 mmHg are predictors of response to terlipressin and albumin in cirrhotic patients with type 1 HRS [83].

The median time to HRS reversal is 7 days, but depends on pre-treatment serum creatinine levels [84]. HRS eventually recurs after discontinuation of treatment in <20% of patients.

Among vasoconstrictor drugs, ***vasopressin analogues*** are considered as the first line therapeutic agents in type 1 HRS.

Vasopressin is a hormone responsible for plasma volume and osmolality regulation acting through different receptors. Among these, V1 receptors are expressed on the vascular smooth muscle cells. The high density of V1 receptors in the splanchnic vascular bed makes these vessels particularly responsive to vasopressin [5].

Terlipressin is a long-acting synthetic vasopressin analogue composite of 1 molecule of lysine vasopressin and 3 glycine residues and it acts by binding to V1 receptors. Terlipressin is administered intravenously at a starting dose of 1 mg/4-6 h. If serum creatinine levels are not reduced of at least 25% of baseline values after 3 days of treatment, the terlipressin dose may be increased to 2 mg/4-6 h with a maximum recommended dose of 12 mg daily [1].

Continuous infusion of terlipressin is associated with a higher response and reduced adverse effect rate compared with bolus injections [66]. Treatment is prolonged for 14 days in case of no response to therapy [1].

The reduction of serum creatinine levels to below 1.5 mg/dL (133 μmol/L) is indicative of a complete response. Terlipressin is contraindicated in severe cardiovascular or ischemic conditions and the patients should be closely monitored for higher risk of arrhythmias, signs of splanchnic or digital ischemia and fluid overload.

The concomitant administration of intravenous albumin is recommended at an initial dose of 1 g/kg body weight, 1 followed by 20-40 g/day [2]. In fact, the association of terlipressin and albumin infusions improves arterial blood pressure, urine output and hyponatremia, ameliorating the neurohormonal abnormalities in 50 to 70% of HRS patients [5].

Noradrenaline is a potent venous and arterial vasoconstrictor by α-adrenergic activity. ***Octreotide*** (a glucagon inhibitor mediates splanchnic vasoconstriction) and ***midodrine*** bind to and activate α1-adrenergic receptors in vascular smooth muscle cells [5].

Noradrenaline or midodrine plus octreotide in association with albumin should be considered as an alternative to terlipressin. Some controlled trials suggested that noradrenaline might be as effective as terlipressin and its lower costs make this treatment an interesting option [66, 85].

Noradrenaline starting dose is 0.5-3 mg/h as continuous intravenous infusion, aimed at an increasing mean arterial pressure of 10 mmHg and/or increase in urine output (>200 mL every 4 h). Treatment should be maintained until serum creatinine levels decrease to 1.5 mg/dL and for a maximum of 15 days [5, 86].

Unfortunately, the number of patients treated with noradrenaline is small and no randomized comparative studies with a control group of patients receiving no vasoconstrictor therapy have been performed to evaluate its efficacy.

Management of type 1 HRS includes midodrine plus ocreotide in combination with albumin. Midodrine is a prodrug metabolized in the liver into desglymidodrine and eliminated by kidney [87]. When given as monotherapy, oral midodrine did not improve systemic hemodynamics and renal function in patients with HRS or with refractory ascites [88].

When associated with octreotide, albumin infusion improves renal function, mean arterial pressure and plasma renin activity [47].

The therapeutic regimen of octreotide, midodrine and albumin significantly improved short-term survival and renal function in HRS type 1 and this may provide a significant benefit for bridging to liver transplantation [87].

Two non-randomized studies evaluated the effect of midodrine and octreotide on HRS, demonstrating reversal of HRS in 70 to 100% of cases treated with this drugs association [47, 89].

Oral midodrine is started at doses of 7.5 mg 3 times daily (with a maximum dose of 12.5 mg 3 times daily) in absence of improvement of renal function [1]. Administration of octreotide is started at doses of 100 μg subcutaneously 3 times daily, with an increase to 200 μg 3 times daily if clinically needed [90].

Ornipressin is a vasopressin analog with potent splanchnic vasoconstrictor action and shown to reverse HRS. This drug requires continuous intravenous administration because of its short half-life and it is commonly associated with ischemic side effects in the splanchnic, muscular and coronary circulation [91].

Renal vasodilators such as dopamine or prostaglandins are ineffective [14, 64, 92].

Patients diagnosed with cirrhosis and hyponatraemia or ascites were eligible for alternative treatment to traditional diuretics.

Vaptans are a class of non-peptide drugs acting as antagonists on arginine vasopressin (AVP) receptors.

AVP acts on its receptors with different mechanism: V1a and V1b receptors are both activated via phospholipase C-mediated pathway, whereas V2 receptors via adenylate cyclase-mediated pathway.

V1a receptors are mainly expressed in vascular smooth muscle cells, liver and brain, mediating the actions of AVP on arterial blood pressure. V1b receptors are present in anterior pituitary and in some extra-pituitary tissues such as brain, kidney and adrenal medulla, acting on the effects of AVP in the release of adrenocorticotrophic hormone. V2 receptors are present in collecting ducts of the kidney, mediating the AVP antidiuretic action, resulting in an increased free water clearance with hypotonic dieresis [5].

Among several antagonists of AVP receptors, the most promising agents of this class are those acting on V2 receptors, non selective (conivaptan) and selective (tolvaptan, satavaptan and lixivaptan).

Conivaptan is a mixed V1/V2-receptor antagonist approved for intravenously administration, able to correct hyponatremia in euvolemic or hypervolemic conditions [93].

Satavaptan, lixivaptan and tolvaptan are oral selective V2 receptor antagonists. The ***Satavaptan*** Investigators Group confirmed its role in improving serum sodium concentration in cirrhotic patients with dilutional (hypervolaemic) hyponatraemia, but showed a limited efficacy in ascites control [94], in contrast with the results of previous phase II studies [95].

Satavaptan is not approved for use outside clinical trials because of adverse effects, such as increased mortality, impaired renal function and prolonged QT interval [96].

Lixivaptan is another selective V2-receptor antagonist that blocks AVP-mediated aquaporin synthesis and membrane insertion [97]. In phase II trials, lixivaptan has increased water excretion, increased serum osmolarity and increased serum sodium concentration in subjects with heart failure, cirrhosis, or SIADH [98-100]. Overall, lixivaptan was considered safe and well-tolerated. Thus, oral lixivaptan can be safely started in the outpatient setting and effectively increases serum sodium concentrations in outpatients with euvolemic hyponatremia [101].

The use of ***tolvaptan*** is approved for hypervolaemic or euvolaemic hyponatriaemia with carefully administration, because this drug increases the bleeding risk, by reduction of vitamin-K-dependent coagulation factors and inhibition of platelet aggregation [102]. Hyponatraemia and ascites are improved through increased excretion of water, but do not affect mortality, cirrhosis or renal failure [96, 103].

Currently, tolvaptan and conivaptan are approved only for the treatment of dilutional hyponatremia (in the USA and Europe) and for volume overload in heart failure (in Japan), but their current costs limit the clinical use, especially compared with lower cost drugs such as classic diuretics. Lixivaptan is a promising and safe agent, even if more consistent trials are needed.

In conclusion, the current data do not suggest the routine use of vaptans in the management of cirrhosis.

SPECIFIC MANAGEMENT OF TYPE 2 HRS

Studies on the effect of vasopressors in association with albumin in patients with type 2 HRS are scarce [104]. The effects of terlipressin in type 2 HRS seem to have a better response rate and longer survival than observed in type 1 [5, 105, 106].

Some studies proposed the use of midodrine, octreotide and albumin in patients with type 2 HRS to improve transplant-free survival, demonstrating no improvement in renal function [89, 104].

An algorithm for management of type 2 HRS, based on current evidences, proposes as a first step the administration of diuretics in patients with sodium excretion under this treatment of >30 mEq/day and an evaluation for liver transplantation.

In these patients, the treatment is based on repeated large-volume paracentesis followed by intravenous administration of albumin (8 g/L) and long-term administration of norfloxacin (at dose of 40 mg/die) to delay HRS and to improve survival [34].

In the case of a progressive increase of serum creatinine, it is necessary to start vasoconstrictors therapy with terlipressin or norepinephrine.

In alternative, it is possible to consider a combination of midodrine and octreotide [2].

Recurrence of HRS after vasoconstrictors discontinuation has been reported, particularly in patients with type 2 HRS and generally retreatment appears to be effective.

Transjugular Intrahepatic Portosystemic Shunt

The effect of transjugular intrahepatic portosystemic shunt (TIPS) insertion on improving urinary sodium excretion and renal function in cirrhotic patients with refractory ascites is well documented [66, 107-110]. Some studies evaluated TIPS placement in patients with type 1 HRS and relatively preserved hepatic function (Child-Turcotte-Pugh score <12). These studies showed HRS reversal and survival for >3 months in ~50% of patients [107].

Hepatic encephalopathy was a common complication following the procedure, although generally with a good response to therapy.

TIPS may be considered in patients without severe liver failure when vasoconstrictors have failed [5, 108]. However,

not all type 1 HRS patients can be treated with this procedure because an elevated serum bilirubin level above 5 mg/dL.

TIPS may improve kidney function and reduce the risk of progression to type 2 HRS [66]. TIPS insertion may prolong survival in HRS patients awaiting liver transplantation, and the time off dialysis in those not candidates for transplantation [109, 110].

In liver-transplanted patients TIPS insertion improves post-transplant outcomes, probably through improving kidney function [111].

Renal Replacement Therapy

Hemodialysis or continuous venovenous hemofiltration have been used as renal-replacement therapy (RRT) in the management of HRS, in particular in patients awaiting transplantation or in those with acute, potentially reversible conditions (e.g. alcoholic hepatitis) [112].

The indications for RRT in HRS patients include volume overload, intractable metabolic acidosis, hyperkalemia not responding to medical therapy or vasoconstrictor drugs inefficacy. Complications such as bleeding, infections and especially hypotension are common during hemodialysis.

In HRS patients waiting for a liver transplant, RRT is justifiable as a bridge to transplantation but is associated with increased morbidity and mortality compared with patients with other forms of acute kidney injury. It is not clear whether RRT will improve the prognosis for patients who are not candidates for a liver transplant [112]. RRT is not indicated in the management of patients with type 2 HRS because of the lack of a severe decrease in kidney function.

Molecular Adsorbent Recirculatory System

An alternative method to conventional RRT is represented by Molecular Adsorbent Recirculatory System (MARS) that stabilizes liver function and improves end-organ damage [113].

In patients with acute-on-chronic liver failure, MARS is associated with a decrease in creatinine and bilirubin levels and an improvement in hepatic encephalopathy when compared with standard therapy, even if a significant beneficial effect on survival could not be demonstrated [114].

In patients with type 1 HRS not responding to treatment with vasoconstrictors, MARS did not show improvement in GFR and RBF [115]. In a study, the use of Prometheus technique (fractioned plasma separation and adsorption) was associated to a significant improvement of survival in patients with type 1 HRS [116]. Nowadays both MARS and Prometheus need more evidence before being considered as therapeutic alternatives in HRS [117].

Liver Transplantation

Liver transplantation is the best treatment for both type 1 and type 2 HRS [2]. Therefore, liver transplantation should be considered in all patients without contraindications to this procedure and it should be performed early because severe renal failure is predictive of a poor outcome after transplantation.

In patients with type 1 HRS orthotopic liver transplantation improves both the liver disease and the associated renal function [118]. Pre-transplantation treatment may improve both the short and long-term outcome after transplantation [119, 120].

Treatment of HRS with albumin and terlipressin before transplantation may be beneficial in the post-transplantation outcome [14].

Paradoxically, a good response to treatment with vasoconstrictors may reduce the baseline MELD score, compromising the position in the transplantation waiting list [121]. For this reason it has been suggested to consider as predictor factor of 3-month survival the baseline MELD score in patients with type 2 HRS responding to pharmacological treatment or, as an alternative, to add other criteria to MELD score, such as serum sodium concentration, hepatic encephalopathy and the cause of renal failure [122,123]. Approximately the 60% of liver transplant after HRS had a complete recovery of kidney function. The renal disease does not improve in the 25% of cases and the remaining 15% of cases has a partially recovered kidney function [5].

Thus, because kidney failure is often reversible after liver transplant, combined liver-kidney transplantation should be considered carefully [124]. Therefore, the indications for combined liver-kidney transplantation are based on guidelines summarized in (Table **4**) [125].

CONCLUSION

HRS is a potentially fatal complication of cirrhosis, characterized by the occurrence of kidney injury in absence of other identifiable causes. The progressive anatomical and functional changes in splanchnic and systemic circulation are typical of advanced stages of liver disease and should promote renal failure in presence of triggering events.

The prevention of renal failure progression is the main goal of HRS treatment and an early identification can improve the prognosis in these patients.

Table 4. Indications for combined liver-kidney transplantation.

Indications for combined liver-kidney transplantation
End-stage renal disease associated with cirrhosis and symptomatic portal hypertension or a hepatic venous pressure gradient of ≥10 mmHg
Acute renal failure or hepatorenal syndrome with serum creatinine levels of ≥2.0 mg/dL (177 μmol/l) and treatment with dialysis for more than 8 weeks
Liver failure and chronic kidney disease with a glomerular filtration rate ≤30 mL/min or more than 30% glomerulosclerosis or fibrosis in a renal-biopsy specimen

The management of HRS patients includes a careful monitoring and prevention of complications (antibiotic prophylaxis), a judicious administration of drugs (vasoconstrictors, diuretics, albumin and fluid administration) and a proper timing of procedures (paracenteses, TIPS or RRT).

Currently, the first line therapy, based on cost and guidelines, is the association of terlipressin and albumin. In alternative, other vasoconstrictors (norepinephrine, ormidodrine) plus octreotide, both in association with albumin may be evaluated in patients with contraindications to terlipressin.

The role of new drugs such as vaptans remains to be established, and among these, lixivaptan seems to be the most promising agent.

Liver transplantation is the best treatment for both types of HRS and in absence of contraindications any patient should be evaluated for a possible inclusion into the transplantation list.

DECLARATION OF INTEREST

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